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EXAMINER	
SCHMIDTMANN, BAHAR	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)
	10/588,409	TIDMARSH, GEORGE
	Examiner	Art Unit
	BAHAR SCHMIDTMANN	1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/19/2007*	6) ☐ Other: _____.

DETAILED ACTION

This application is a 35 U.S.C. § 371 National Stage Filing of International Application No. PCT/US05/03370, filed 04 February 2005, which claims priority under 35 U.S.C. §119(e) to US Provisional Application No. 60/542494, filed 06 February 2004.

The preliminary amendments filed 03 August 2006 is acknowledged. Claims 1-20 are pending in the current application and are examined on the merits herein.

Information Disclosure Statement

The Information Disclosure Statement submitted 19 October 2007 is acknowledged and considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briasoulis et al. (*European Journal of Cancer*, May 2003, vol. 39, pp.2334-2340, cited in PTO-892) in view of Giaccone et al. (*European Journal of Cancer*, January 2004, vol. 40, pp.667-672, cited in PTO-892).

Briasoulis et al. teaches glufosfamide can be administered using a 1-hour infusion as first-line treatment for advanced pancreatic cancer (title). Briasoulis et al.

teaches patients were administered 5 g/m^2 of the glufosfamide once every three weeks (abstract; also see p. 2335, left column, last paragraph). Briasoulis et al. teaches that the glufosfamide can also be administered over a 6-hour infusion time (p.2335, right column, second paragraph). Briasoulis et al. teaches the patients treated had metastatic or inoperable (i.e. refractory) locally advanced disease (p.2335, right column, *2.2. Patient registration*). Briasoulis et al. teaches patients were treated for one to six cycles (p.2336, left column, first paragraph). Briasoulis et al. teaches gemcitabine is a known reference chemotherapeutic agent for advanced pancreatic cancer, especially in comparison to 5-fluorouracil (p.2335, left column, first paragraph). Briasoulis et al. concludes from the phase II trials that glufosfamide has modest activity against advanced/metastatic pancreatic cancer and that the response rate and duration of survival are comparable to gemcitabine (p.2339, first three paragraphs).

Briasoulis et al. does not expressly disclose administering glufosfamide to a subject in need of treatment for a chemotherapy-refractory pancreatic cancer (instant claims 16-20).

Giaccone et al. teaches administering glufosfamide by 1-hour infusion as a second-line treatment for advanced non-small cell lung cancer (title). Giaccone et al. teaches administering 5 g/m^2 by a 1-hour infusion every 3 weeks (abstract). Giaccone et al. teaches the purpose of the study was to administer glufosfamide in advanced NSCLC patients pretreated by chemotherapy (p.668, *2.1. Study design—objectives*).

It would have been obvious at the time the invention was made to administer glufosfamide to a subject having chemotherapy-refractory pancreatic cancer.

MPEP 2141 states, "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusatory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S. at ,82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) " Obvious to try " choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Based on the teachings of the MPEP and KSR above, by employing the rationale in (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention; one having ordinary skill in the art would have been motivated to administer glufosfamide to a subject having chemotherapy-refractory pancreatic cancer. From Briasoulis et al., it was known at the time the invention was made that glufosfamide has efficacy against advanced metastatic pancreatic cancer. And as suggested by Giacconne et al., if advanced cancer is ineffective to known chemotherapeutics like gemcitabine, a person having ordinary skill in the art would have known to administer glufosfamide since this has been successfully demonstrated on chemotherapy-refractory cancer patients.

The skilled artisan was taught gemcitabine was known to be clinically relevant in chemotherapy-based treatment of advanced pancreatic cancer and advanced non-small cell lung cancer. The skilled artisan would have known that glufosfamide demonstrated anti-tumorous activity on similar levels as gemcitabine in treating pancreatic cancer, wherein said gemcitabine was known to be "accepted as the reference chemotherapeutic agent for advanced pancreatic cancer on the basis of its superiority with regard to clinic benefit response" (p.2335, left column, first paragraph). For that reason, glufosfamide is an art recognized equivalent to gemcitabine. Glufosfamide has been proven effective as a first-line chemotherapy agent as taught by Briasoulis et al. and a second-line chemotherapy agent for patients having chemotherapy-refractory cancer by Giaccone et al. Because of its art recognized equivalence and because it

has been demonstrated to be clinically useful in multiple locally advanced cancers including phase II clinical trials against advanced pancreatic cancer, a person having ordinary skill in the art would have been motivated to administer glufosfamide to a person having chemotherapy-refractory pancreatic cancer.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teaching of the prior art.

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noble et al. (*Drugs*, 1997, vol. 54, no. 3, pp.447-472, cited by Applicant in Information Disclosure Statement) in view of Briasoulis et al. (cited above) and Kozuch et al. (*The Oncologist*, 2001, vol. 6, pp.488-495, cited by Applicant in Information Disclosure Statement) and in further view of Giaconne et al. (cited above).

Noble et al. teaches gemcitabine was effective in treating patients having advanced pancreatic cancer that were surgery or radiotherapy-refractory pancreatic cancer patients (p.460, *3.2 Pancreatic Cancer*). Noble et al. teaches other dosage regiments of gemcitabine include 1000 mg/m^2 once a week for seven weeks, followed by a one week rest (seven week *dosage* cycle) and then once a week for three weeks with a one week rest (four week cycle), (p.461, table VII). Noble et al. teaches that gemcitabine should be administered in 30 minute infusions (p.465, last paragraph). Noble et al. teaches combined therapy with gemcitabine and fluorouracil has been used in patients with advanced pancreatic cancer (p.469, second paragraph). Noble et al.

suggests that this combination and others involving gemcitabine and other chemotherapeutic agents should be explored in the future (p.469, second paragraph).

Noble et al. teaches chemotherapy regiments directed at treating non-small lung cancer comprising administering gemcitabine combinations with ifosfamide, wherein the gemcitabine was administered by infusion at 1000 mg/m^2 once weekly for 3 of 4 weeks and ifosfamide was administered by infusion at 1500 mg/m^2 on days 8 to 12 of a 28 day cycle (p.457, last paragraph). Noble et al. teaches this combination resulted in an objective response rate of 22% for NSLC (p.457, last paragraph).

Noble et al. does not expressly disclose administering a combination of *glu*fosfamide with gemcitabine (instant claims 1-15). Noble et al. does not expressly disclose the order of administration (instant claims 8, 9 and 13-15).

Briasoulis et al. teaches as discussed above.

Kozuch et al. teaches the efficacy of doublet combinations of gemcitabine, ironotecan, cisplatin and 5-fluorouracil have been successful in patients having advanced pancreatic cancer (p.489, left column, second paragraph). Kozuch et al. teaches gemcitabine was the first drug approved for the treatment of pancreatic cancer and has a favorable toxicity profile (p.491, last paragraph). Kozuch et al. teaches gemcitabine-based doublets with 5-fluorouracil, cisplatin and irinotecan are feasible and the data suggests consistent improved response rates, response duration, overall survival and quality of life compared with gemcitabine alone (p.492, first paragraph). Kozuch et al. teaches gemcitabine-based combination therapy involves administering

gemcitabine on the same day as the other chemotherapeutic drugs (p.490, first paragraph).

Giaccone et al. teaches as discussed above.

It would have been obvious at the time the invention was made to administer a combination of gemcitabine and glufosfamide to a patient having advanced pancreatic cancer.

Based on the teachings of the MPEP and KSR above, by employing the rationale in (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention; one having ordinary skill in the art would have been motivated to administer a combination of gemcitabine and glufosfamide to a patient having advanced pancreatic cancer.

A person having ordinary skill in the art would have known at the time the invention was made from all of the cited references, that gemcitabine is a leading chemotherapeutic agent used in the treatment of locally advanced pancreatic and non-small cell lung cancer. Noble explicitly teaches gemcitabine combination therapy is useful against non-small cell lung cancer, and explored as a means for treating advanced pancreatic cancer. This reference encouraged those of ordinary skill in the art to explore gemcitabine combinations with known and novel chemotherapeutic agents. It should be noted that one of the combinations mentioned includes gemcitabine with ifosfamide, wherein glufosfamide as instantly claimed is simply a beta-glucose derivative of ifosfamide. The skilled artisan would have known from Noble that

this specific combination did in fact provide some success in the treatment of non-small cell lung cancer, a locally advanced cancer.

Kozuch et al. actually demonstrates what Noble suggested, that gemcitabine chemotherapeutic combinations can be useful in treating advanced pancreatic cancer. From Briasoulis and Giaccone et al., respectively, the skilled artisan would have known at the time the invention was made that glufosfamide, a derivative of ifosfamide can be effective in treating advanced pancreatic cancer and non-small cell lung cancer. Briasoulis et al. goes on to teach that glufosfamide can be useful as a first-line chemotherapeutic agent and Giaccone et al. teaches that glufosfamide can also be useful as a second-line chemotherapeutic agent.

As discussed above, the prior art recognizes both gemcitabine and glufosfamide as art equivalents in the treatment of advanced pancreatic cancer. The art also strongly suggests and teaches gemcitabine-based combinations. More notably, Noble teaches a combination of gemcitabine with ifosfamide, wherein glufosfamide is a beta-glucose derivative of ifosfamide. Both gemcitabine and glufosfamide have been successfully used to treat advanced pancreatic cancer. Thus in view of their common therapeutic utility, a suggestion in the prior art to administer gemcitabine-based combinations and in view of the success in treating locally advanced cancer by administering gemcitabine with ifosfamide, one having ordinary skill in the art would have been motivated to administer a combination of both gemcitabine and glufosfamide to a person having locally advanced cancer and more specifically to a person having advanced pancreatic cancer.

From Kozuch et al., the skilled artisan would have known at the time the invention was made that gemcitabine can be administered sequentially on the same day as other known chemotherapeutic agents in combination-based therapy. Additionally, a person having ordinary skill in the art would have known that both gemcitabine and glufosfamide are art recognized equivalents and would have been motivated to administer both drugs on the same day to provide maximum effect in killing the tumorous cells. Because it was known to sequentially administer gemcitabine with other chemotherapeutics, it would have been obvious to administer the gemcitabine before or after the glufosfamide infusion.

Combination of the two drugs would also necessarily require optimization of dosage frequency and is well within the level of ordinary skill in the art. For example, the prior art teaches administering glufosfamide at 5 g/m^2, which is broadly and reasonably considered about 4.5 g/m^2, over an infusion period of 1-hour every three weeks. However, it is also known that gemcitabine administration can be given in four week cycles wherein the drug is actively infused for the first three weeks followed by a resting week. Therefore, it would have been obvious to modify the administration of glufosfamide in a gemcitabine based combination-based therapy such that it is also provided once every four weeks instead of every three weeks.

Additionally, from Briasoulis et al., one having ordinary skill in the art would have known that glufosfamide can be administered by infusion over 1 to 6-hours. Therefore, it would have been obvious to administer the glufosfamide over 4 hours.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teaching of the prior art.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. BAHAR SCHMIDTMANN whose telephone number is (571)270-1326. The examiner can normally be reached on Mon-Thurs 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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